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Direct inhibitory effect of calcitriol on parathyroid function (sigmoidal curve) in dialysis

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Direct inhibitory effect of calcitriol on parathyroid function (sigmoidal curve) in dialysis. The effect of intravenous calcitriol on parathyroid function was evaluated in nine chronic hemodialysis patients with secondary hyperparathyroidism. Two micrograms of calcitriol were administered intravenously after dialysis thrice weekly for ten weeks. Parathyroid function was assessed by inducing hypo- and hypercalcemia with low calcium (1.0 mEq/liter) and high calcium (4.0 mEq/liter) dialyses before and after ten weeks of intravenous calcitriol therapy. To avoid hypercalcemia during calcitriol administration, the dialysate calcium was reduced to 2.5 mEq/liter. Parathyroid hormone (PTH) values (pg/ml) from dialysis-induced hypo- and hypercalcemia were plotted against serum ionized calcium, and the sigmoidal relationship between PTH and calcium was evaluated. Basal PTH levels fell from 902 ± 126 pg/ml to 466 ± 152 pg/ml ($P < 0.01$) after therapy without a significant change in the serum total calcium concentration. The ionized calcium-PTH sigmoidal curve shifted to the left and downward after calcitriol therapy. The maximal PTH response during hypocalcemia decreased after calcitriol from 1661 ± 485 pg/ml before calcitriol to 1031 ± 280 pg/ml afterward ($P < 0.05$). The PTH level at maximal inhibition due to hypercalcemia decreased from 281 ± 76 pg/ml before calcitriol to 192 ± 48 pg/ml afterward ($P < 0.05$). The slope of the sigmoidal curve changed from −2125 ± 487 to −1563 ± 385 ($P < 0.05$). The set point of ionized calcium (4.60 ± .11 mg/dl before vs. 4.44 ± .07 mg/dl after) did not change significantly with calcitriol therapy. In summary, ten weeks of intravenous calcitriol therapy decreased PTH secretion across a wide range of serum ionized calcium concentrations, shifting the ionized calcium-PTH sigmoidal curve toward normal (left and downward). There were no significant changes in basal serum total calcium concentration throughout the study. These results demonstrate a direct inhibitory effect of intravenous calcitriol on parathyroid function in dialysis patients with secondary hyperparathyroidism.

The most common form of renal osteodystrophy present in maintenance hemodialysis patients is osteitis fibrosa [1]. This is characterized by increased bone formation and resorption, as well as elevated parathyroid hormone (PTH) levels, and may be present in early renal failure [2–4].

Calcitriol deficiency may contribute to the development and maintenance of secondary hyperparathyroidism in dialysis patients. Calcitriol receptors are abundant in the parathyroid gland and studies in parathyroid gland cell cultures have shown mRNA coding for preproparathyroid hormone to be suppressed by the addition of calcitriol to the cell cultures [5, 6]. Thus, in addition to hypercalcemia induced by calcitriol, a direct inhibitory effect of calcitriol, independent of hypercalcemia, may be important in the regulation of parathyroid gland activity [7]. Oral calcitriol therapy in dialysis patients with osteitis fibrosa has been shown to decrease PTH levels [8]. This suppressant effect of calcitriol on plasma PTH levels was assumed to be secondary to the development of hypercalcemia. However, recent data have demonstrated that the intravenous administration of calcitriol to dialysis patients with osteitis fibrosa markedly reduced PTH levels [9]. These findings suggested the possibility that calcitriol may directly inhibit PTH secretion. However, most of the observed decrease in PTH levels occurred at a time when the serum calcium level was increasing. Thus, since the calcium-PTH relationship is not linear, the possibility that an increase in the serum calcium concentration may have been responsible for the PTH inhibition could not be entirely excluded.

The concept of PTH secretion in relation to the set point of calcium (defined as the calcium level at which maximal PTH secretion is suppressed by 50%) has been developed as a parameter of parathyroid gland sensitivity [10]. When parathyroid glands from patients with secondary hyperparathyroidism were studied in vitro, an elevated set point of calcium for PTH secretion was demonstrated [11, 12]. When the set point is increased, a higher calcium concentration is required to inhibit PTH secretion. We have shown that during a calcium free dialysis some patients with osteitis fibrosa markedly increased PTH secretion while the serum calcium remained greater than 9 mg/dl [13]. These observations suggest that the set point of calcium may be abnormal in dialysis patients with osteitis fibrosa. The possible role of calcitriol in the pathogenesis or correction of the abnormal set point has not been previously evaluated.

The aim of the present study was to evaluate in dialysis patients with secondary hyperparathyroidism: a) whether a direct effect of calcitriol on PTH secretion (independent of hypercalcemia) is present; and b) the effect of intravenous calcitriol on parathyroid function and the set point of calcium for PTH secretion.

Methods

Nine stable patients on maintenance hemodialysis who had never received calcitriol or vitamin D analogues were studied. All patients had at least a 10-fold elevation of serum PTH, serum aluminum levels less than 50 μg/liter, and/or histological

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evidence of osteitis fibrosa with less than 5% stainable bone aluminum. Patients were dialyzed 3-1/2 to 4 hours, three times per week, and continued on aluminum-containing phosphate binders throughout the study period. Dietary calcium remained constant throughout the study.

Prior to administration of calcitriol, a low calcium dialysis (dialysate calcium of 1.0 mEq/liter) was performed to induce hypocalcemia. Hypocalcemia induced in this manner has been shown to maximally stimulate PTH secretion [13]. Serum calcium and PTH were sampled at the start of the low calcium dialysis and every 30 minutes throughout the dialysis treatment. The following week, a high calcium dialysis (dialysate calcium of 4 mEq/liter) was performed to induce mild hypercalcemia and maximally inhibit PTH secretion. Serum calcium and PTH were obtained at baseline and every 30 minutes throughout the dialysis. Serum chemistries, including phosphate, alkaline phosphatase, total protein, albumin, and electrolytes were obtained immediately before the low calcium dialysis.

Following the baseline studies, patients were treated with 2 μg of intravenous calcitriol at the end of each dialysis for the next ten weeks. During this time, the dialysate calcium was reduced to 2.5 mEq/liter to prevent the development of hypercalcemia (14). Serum calcium and phosphate measurements were obtained weekly prior to analysis. If the serum calcium exceeded 10 mg/dl, the calcitriol dosage was reduced. Only two patients required a reduction of calcitriol to 1 μg, after six and eight weeks of therapy, respectively. Parathyroid hormone, alkaline phosphatase, total protein, albumin, and electrolyte determinations were made weekly. After ten weeks of calcitriol therapy, the low and high calcium dialyses were repeated as outlined above.

From the data obtained during dialysis-induced hypo- and hypercalcemia, individual serum ionized calcium-PTH sigmoidal curves were constructed for each patient before and after calcitriol therapy. Composite serum calcium-PTH curves for the group were compiled from the individual curves obtained before and after treatment with calcitriol. The PTH values on the composite curve (Fig. 2) at each calcium increment are the mean for the group of PTH values obtained from each individual curve at that particular calcium concentration.

For analysis and interpretation of the serum calcium-PTH curve the following terms are defined as follows: maximal PTH stimulation is the highest PTH level observed in response to hypocalcemia; maximal PTH inhibition is the lowest PTH concentration during suppression by hypercalcemia; the slope of the sigmoidal curve is the PTH value at maximal PTH stimulation minus the PTH value at maximal PTH inhibition divided by the difference of the serum calcium concentration at maximal PTH stimulation minus the serum calcium concentration at the maximal PTH inhibition; the set point of calcium is the serum calcium concentration at which maximal PTH secretion is reduced by 50%.

Anterior iliac crest bone biopsies were performed in eight patients. Bone specimens were processed as previously described and stained for aluminum by the method of Maloney et al (15). Stainable trabecular bone aluminum was less than 5% in all patients.

Intact parathyroid hormone was measured with an intact hormone radioimmunoassay (Allegro, Nichols Institute, San Juan Capistrano, California, USA) [16, 17]. Normal values are

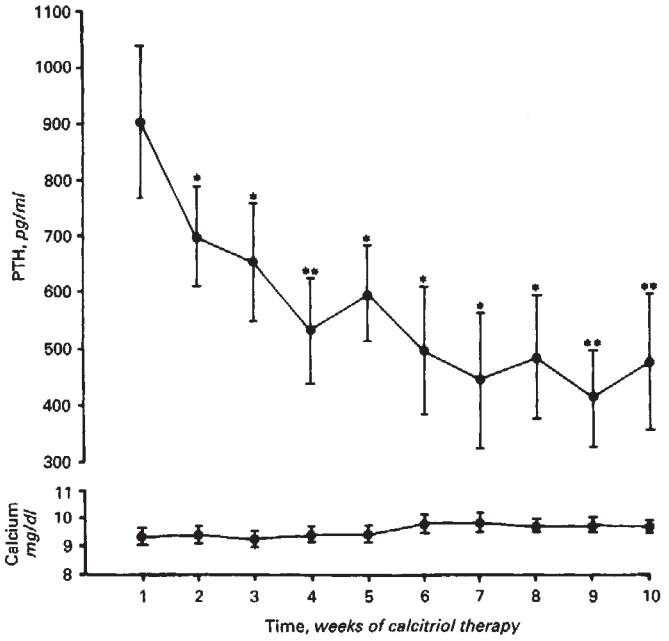

Fig. 1. *Baseline PTH and total serum calcium levels during the ten weeks of intravenous calcitriol therapy are shown.* *$P < 0.05$ vs. baseline; (**) $P < 0.01$ vs. baseline.

10 to 65 pg/ml. Serum ionized calcium was evaluated using an ICA 1 ionized calcium analyzer (Radiometer A/S, Copenhagen, Denmark). Total serum calcium was determined by atomic absorption spectrophotometry (Perkin-Elmer Corporation, Norwalk, Connecticut, USA, model 5300). Serum phosphate, alkaline phosphatase, total protein, albumin, and electrolytes were measured by a Technicon SMA II autoanalyzer (Technicon Instruments Corporation, Tarrytown, New York, USA). Serum aluminum was determined by flameless atomic absorption spectrophotometry as previously described [18].

Informed consent was obtained from each patient in a protocol approved by the Institutional Review Board of the University of Oklahoma Health Sciences Center and the Oklahoma City Veterans Administration Medical Center.

Data was analyzed by Student's t-test for paired comparisons and analysis of variance for repeated measures. Results are expressed as mean ± SE.

Results

The study population consisted of nine maintenance hemodialysis patients, of whom one was female. The mean age (± SE) was 56.6 ± 2.5 years and the length of time on dialysis was 33.7 ± 7.5 months.

The mean baseline serum PTH level was markedly elevated at 902 ± 126 pg/ml. As shown in Figure 1, treatment with calcitriol resulted in a gradual decrease of the high serum PTH levels to 466 ± 152 pg/ml by the end of ten weeks, $P < 0.01$. This occurred even though the serum total calcium did not change significantly (9.36 ± 0.28 to 9.68 ± 0.16 mg/dl). Other laboratory findings were not altered by calcitriol therapy (Table 1). The mean serum albumin and total protein levels before and after treatment were similar. The mean serum phosphate level also remained unchanged and the mean serum alkaline phos-

Table 1. Biochemical data (mean ± SE) before and after calcitriol therapy

	Week 1	Week 10
Calcium *mg/dl*	9.36 ± 0.28	9.68 ± 0.16[a]
Albumin *g/liter*	41.5 ± 1.3	40.5 ± 0.9[a]
Total protein *g/liter*	70.3 ± 1.3	70.5 ± 2.8[a]
PO_4 *mg/dl*	7.86 ± 0.95	7.81 ± 0.43[a]
HCO_3 *mEq/liter*	16.7 ± 0.8	19.2 ± 1.3[b]
Alk phos *IU/liter*	211.2 ± 59.4	172.0 ± 34.7[a]

[a] No significant difference between Weeks 1 and 10
[b] $P < 0.05$ compared to Week 1

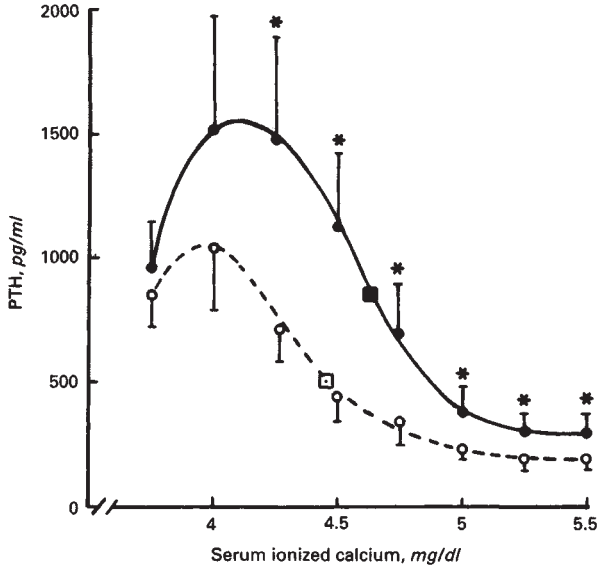

Fig. 2. *The sigmoidal serum ionized calcium-PTH curve before (solid line) and after (dashed line) ten weeks of intravenous calcitriol therapy is shown.* The set point is represented by a solid square before and an open square after calcitriol.

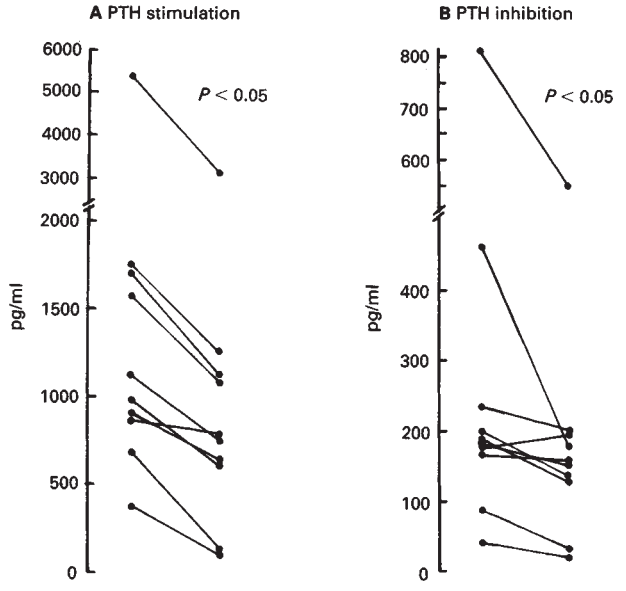

Fig. 3. *Changes before and after calcitriol therapy in maximal stimulated PTH levels during hypocalcemia (A) and maximally inhibited PTH levels by hypercalcemia (B) are shown.*

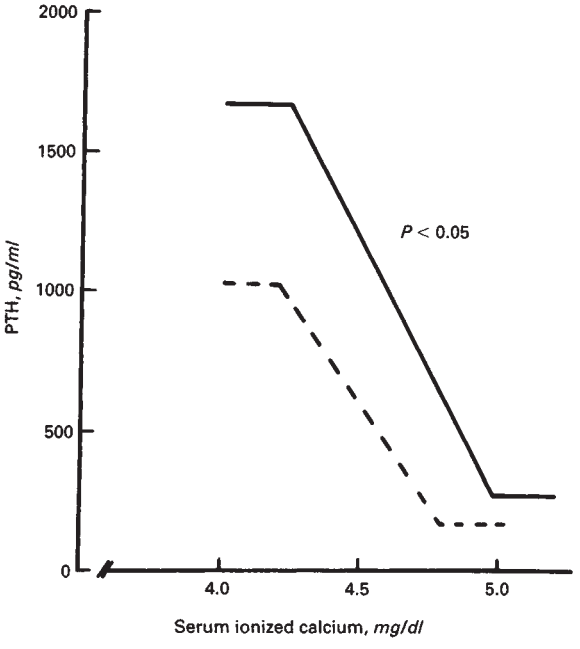

Fig. 4. *The change in the slope of the sigmoidal calcium-PTH curve before and after (---) ten weeks of intravenous calcitriol therapy is presented.*

phatase level declined slightly. The serum bicarbonate concentration increased during the study period ($P < 0.05$). No significant change was seen in the baseline ionized calcium, which was 4.49 ± 0.11 mg/dl before calcitriol versus 4.40 ± 0.06 mg/dl after treatment.

Changes in the serum ionized calcium-PTH sigmoidal curve before and after calcitriol therapy are shown in Figure 2. Before calcitriol, the sigmoidal curve was shifted to the right and upward when compared with normal patients [17]. After calcitriol, the serum PTH concentration was lower for each serum calcium level throughout the entire range of serum calcium concentrations; this is reflected by a shift of the curve downward and to the left. Progressive hypocalcemia after maximal PTH levels had been attained resulted in a decrease in the PTH concentration. As shown in Figure 3, the maximal PTH response induced during hypocalcemia decreased significantly after calcitriol from 1661 ± 485 to 1031 ± 280 pg/ml, $P < 0.05$. Also presented in Figure 3, the PTH level at maximal suppression during hypercalcemia decreased from 281 ± 78 to 192 ± 48 pg/ml, $P < 0.05$. The slope of the sigmoidal curve decreased significantly from −2125 ± 487 to −1563 ± 385, $P < 0.05$ (Fig. 4). The serum ionized calcium concentrations before and after calcitriol at which maximal PTH stimulation (4.24 ± 0.11 vs. 4.20 ± 0.09 mg/dl) and inhibition (4.96 ± .10 vs. 4.79 ± 0.09 mg/dl) occurred were similar. The set point of calcium did not change significantly after ten weeks of intravenous calcitriol administration (Fig. 5). Thus, before calcitriol, the set point was 4.60 ± 0.11 mg/dl and after calcitriol 4.45 ± 0.07 mg/dl.

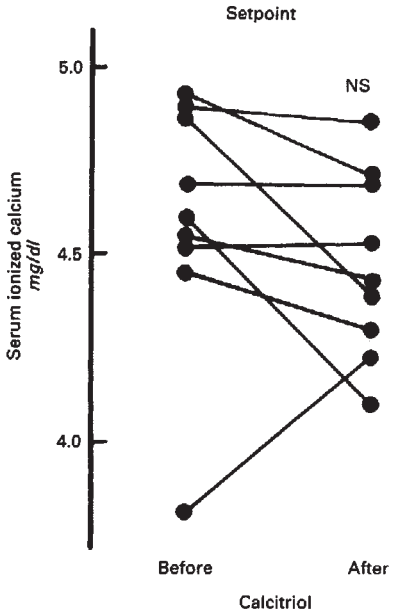

Fig. 5. *The set point of calcium (defined as the serum calcium level at which maximal PTH secretion is reduced by 50%) before and after calcitriol is shown for each individual patient.*

Discussion

In the present study, ten weeks of thrice weekly intravenous calcitriol significantly decreased PTH levels. Basal PTH levels decreased in the absence of hypercalcemia. Furthermore, after calcitriol therapy, the slope of the ionized calcium-PTH curve decreased as a result of a reduction in the amount of PTH produced during maximal stimulation and inhibition. These findings strongly suggest a direct inhibitory effect of calcitriol on PTH secretion. However, although there was a decrease in the set point of calcium, it was not significant.

Slatopolsky et al have shown significant suppression of basal PTH levels following intravenous calcitriol therapy in dialysis patients with secondary hyperparathyroidism [9]. The authors attributed some of the inhibitory effect of calcitriol on PTH secretion to the increase in serum calcium observed during the study period. However, their subjects showed a 20% decrease in PTH levels prior to the increase in the serum calcium concentration. Our results show that basal PTH levels declined without a significant change in the serum calcium. Furthermore, our results extend those of other clinical studies by demonstrating that after calcitriol, PTH levels were decreased throughout a wide range of serum calcium concentrations [8, 9, 19]. Thus, at both maximal stimulation and maximal inhibition, serum PTH levels were lower after calcitriol therapy. Our patients' serum phosphate levels were elevated, indicating noncompliance with their prescribed phosphate binder. A greater reduction in PTH levels during calcitriol therapy might be seen in a more compliant population.

Parathyroid glands p ɔssess abundant calcitriol receptors, and calcitriol is known to inhibit the synthesis of preproparathyroid hormone [5, 6]. The use of intravenous calcitriol after each hemodialysis treatment may lead to inhibition of the cellular translation and transcription processes needed to produce the increased amounts of PTH that characterize osteitis fibrosa. In addition, calcitriol has been shown to increase cytosolic calcium in parathyroid cell cultures; this effect may augment the suppression in PTH secretion observed with calcitriol [20, 21]. The decrease in serum PTH observed in this study suggests that the parathyroid glands do not escape the effects of calcitriol in the 48 to 72 hours between doses. The biologic half-life of calcitriol is six to ten hours [22]. Thus, calcitriol behaves as a classic steroid hormone, with metabolic actions far outlasting its plasma half-life. The clinical implication for the hemodialysis patient with osteitis fibrosa is that two micrograms of calcitriol administered intravenously thrice weekly may be sufficient to significantly inhibit PTH secretion.

The level of PTH achieved during maximal stimulation of the parathyroid gland with hypocalcemia decreased substantially after ten weeks of intravenous calcitriol administration. Since parathyroid gland mass correlates directly with maximal PTH secretion [23], this suggests that calcitriol therapy leads to a decrease in functional parathyroid gland mass. This could be due to either a decrement in the amount of PTH produced by each cell, a quantitative shift in the subset of cells from active production and secretion to quiescence, or a combination of the above mechanisms. After maximal PTH stimulation was achieved during progressive hypocalcemia, there was a decrease in PTH levels. This phenomenon has been described previously, and most likely is due to depletion of stored hormone [24].

The inhibition of PTH secretion induced by hypercalcemia was greater after calcitriol therapy as compared with pretreatment values. This may reflect a decrease in non-suppressible parathyroid gland activity [25]. The calcium level at which the parathyroid glands were maximally inhibited did not change. The mechanisms underlying the decrease in PTH secretion during both hyper- and hypocalcemia may be similar.

The slope of the sigmoidal curve of the ionized calcium-PTH relationship decreased with calcitriol therapy. This change was secondary to the decrease in maximally stimulated and inhibited PTH secretion.

The set point of ionized calcium for PTH secretion did not change with intravenous calcitriol therapy. An increase in the set point leads to an increase in PTH secretion at a given concentration of calcium; the opposite would occur if the set point was decreased [26]. Our results indicate that calcitriol did not affect the set point; however, it is possible that the lack of effect may be due to the short duration of calcitriol therapy in our study, or to the small number of patients studied. There was a trend toward a decrease in the set point of calcium. In fact, the mean set point of calcium would have decreased significantly if we had removed from the study the only patient who demonstrated an increase in the set point (Fig. 5).

Ionized calcium-PTH curves were recently reported in normal subjects by Brent et al, who used the same PTH assay to study PTH secretion in response to EDTA and calcium infusions [17]. They observed much smaller values for PTH during maximal stimulation (99 to 125 pg/ml) and maximal inhibition (<10 pg/ml) than those noted in our study. Also, maximal stimulation and inhibition of PTH secretion were achieved at lower serum calcium concentrations in their normal patients when compared with our subjects with secondary hyperparathyroidism. In addition, these authors noted that the PTH

response to hypo- and hypercalcemia was not dependent on the rate of change in the extracellular calcium concentration.

Our observations differ from the findings of Delmez et al, who reported a decrease in the set point of calcium for PTH secretion after two weeks of intravenous calcitriol therapy [27]. However, in that study the set point was calculated as the ionized calcium concentration at which baseline PTH values were reduced by 50%. In the present study, the set point is calculated according to the method of Brown et al, as the serum calcium concentration at which maximal PTH secretion is reduced by 50% [11].

In the past, calcitriol was thought to indirectly inhibit PTH secretion by increasing the serum calcium concentration, bone resorption [28, 29]. Recently, Yamamoto et al demonstrated that changes in serum calcium concentrations regulate not only the secretion, but also the biosynthesis, of PTH [30]. In addition to the indirect effects of calcitriol, the present study strongly suggests that intravenous calcitriol directly inhibits PTH secretion. The effect of calcitriol on the parathyroid gland may be maximized by intravenous administration of this hormone, as compared with the oral route because of the higher serum concentration of calcitriol achieved with the intravenous route. Thus, for the same dose of calcitriol, fourfold higher serum levels are achieved with an intravenous preparation, as compared to the oral route [9]. Furthermore, calcitriol is hepatically metabolized, and less drug may be available to target tissues outside the gut if the drug is given orally [31].

There was a significant increase in serum bicarbonate concentration after calcitriol therapy. The reason for such increment is not apparent. Nevertheless, theoretically an increment in serum bicarbonate may decrease serum ionized calcium; thus, it may have played a role in the final serum ionized calcium after calcitriol therapy.

In summary, ten weeks of thrice-weekly intravenous calcitriol therapy ameliorated secondary hyperparathyroidism in our patients, by directly inhibiting PTH secretion. Calcitriol produced a shift of the sigmoidal ionized-calcium PTH curve to the left and downward. Although the set point of calcium did not change, the slope of the calcium-PTH curve decreased. In conclusion, intravenous calcitriol directly inhibits PTH secretion and may be an effective treatment for secondary hyperparathyroidism in maintenance dialysis patients. Long-term studies to evaluate the therapeutic benefit of intravenous calcitriol in dialysis patients with secondary hyperparathyroidism are indicated.

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